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- (71) Applicant (*for all designated States except US*): MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 40 Landsdowne Street, Cambridge, MA 02139 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): KELLY, Louise, M. [IE/US]; 1450 Beacon Street, Apt. 703, Brookline, MA 02446 (US). CARROLL, Joseph, M. [US/US]; 113 Sciarappa St., Cambridge, MA 02141 (US). FARLOW, Deborah [US/US]; 245 Main Street, Apt. 18, Watertown, MA
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(54) Title: METHODS AND COMPOSITIONS FOR TREATING HEMATOLOGICAL DISORDERS USING 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 OR

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of hematological disorders. Specifically, the present invention identifies the differential expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 and 5014 genes in tissues relating to hematological disorders sensation, relative to their expression in normal, or non-hematological disorders disease states, and/or in response to manipulations relevant to hematological disorders. The present invention describes methods for the diagnostic evaluation and prognosis of various hematological disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating hematological disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of hematological disorders.

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**METHODS AND COMPOSITIONS FOR TREATING HEMATOLOGICAL  
DISORDERS USING 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620,  
21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891,  
9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661,  
16052, 1521, 6662, 13913, 12405 OR 5014**

**Related Applications**

[0001] The present application claims the benefit of U.S. Provisional Application Serial No. 60/445,241, filed on February 5, 2003, of U.S. Provisional Application Serial No. 60/448,389, filed on February 18, 2003, of U.S. Provisional Application Serial No. 60/456,320, filed on March 20, 2003, of U.S. Provisional Application Serial No. 60/460,279, filed on April 3, 2003, of U.S. Provisional Application Serial No. 60/465,924, filed on April 28, 2003, of U.S. Provisional Application Serial No. 60/470,052, filed on May 13, 2003, of U.S. Provisional Application Serial No. 60/498,106, filed on August 26, 2003, of U.S. Provisional Application Serial No. 60/500,179, filed on September 4, 2003, of U.S. Provisional Application Serial No. 60/502,909, filed on September 15, 2003, of U.S. Provisional Application Serial No. 60/510,351, filed on October 10, 2003, and of U.S. Provisional Application Serial No. 60/512,380, filed on October 17, 2003. The entire contents of these provisional patent applications are hereby incorporated in their entirety by this reference.

**Background of the Invention**

[0002] Targets involved in the regulation of bone marrow development provide novel therapeutic approaches to the treatment of primary bone marrow failure and bone marrow dysfunction secondary to toxic insults, most notably chemotherapy-induced cytopenias. There is a severe unmet medical need in this arena as the few therapies currently available are recombinant proteins and all act at a relatively late stage of lineage differentiation.

[0003] Marrow populations of human and murine origin enriched for hematopoietic stem cells as well as bone marrow stromal cell populations provide useful sources of material for gene discovery and annotation of targets involved in proliferation and maturation of precursor populations. Hematopoietic cells cultured under various

circumstances, isolated from humans in vivo, or from animal models in vivo provide a rich source of raw material for gene expression analysis leading to the identification of novel therapeutics useful for hematological disorders.

### **Detailed Description of the Invention**

[0004] The present invention provides methods and compositions for the diagnosis and treatment of patients with hemtological disorders.

[0005] "Treatment", as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or affecting the disease or disorder, at least one symptom of disease or disorder or the predisposition toward a disease or disorder. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Representative molecules are described herein.

[0006] A hematological disorder as used herein includes, but is not limited to erythroid-associated disorders. As used herein, the term "erythroid associated disorders" include disorders involving aberrant (increased or deficient) erythroblast proliferation, e.g., an erythroleukemia, and aberrant (increased or deficient) erythroblast differentiation, e.g., an anemia. Erythrocyte-associated disorders include anemias such as, for example, drug-(chemotherapy-) induced anemias, hemolytic anemias due to hereditary cell membrane abnormalities, such as hereditary spherocytosis, hereditary elliptocytosis, and hereditary pyropoikilocytosis; hemolytic anemias due to acquired cell membrane defects, such as paroxysmal nocturnal hemoglobinuria and spur cell anemia; hemolytic anemias caused by antibody reactions, for example to the RBC antigens, or antigens of the ABO system, Lewis system, Ii system, Rh system, Kidd system, Duffy system, and Kell system; methemoglobinemia; a failure of erythropoiesis, for example, as a result of aplastic anemia, pure red cell aplasia, myelodysplastic syndromes, sideroblastic anemias, and congenital dyserythropoietic anemia; secondary anemia in non-hematologic disorders, for example, as a result of chemotherapy, alcoholism, or liver disease; anemia of chronic disease, such as chronic renal failure; and endocrine deficiency diseases.

[0007] Agents that modulate the polypeptides of the present invention or nucleic acid activity or expression can be used to treat anemias, in particular, drug-induced

anemias or anemias associated with cancer chemotherapy, chronic renal failure, malignancies, adult and juvenile rheumatoid arthritis, disorders of hemoglobin synthesis, prematurity, and zidovudine treatment of HIV infection. A subject receiving the treatment can be additionally treated with a second agent, e.g., erythropoietin, to further at least one symptom of the condition. The order of the treatments can be reversed. The two treatments can be administered simultaneously. The timing between treatments can be varied.

[0008] As used herein, the term "erythropoietin" or "EPO" refers to a glycoprotein produced in the kidney, which is the principal hormone responsible for stimulating red blood cell production (erythropoiesis). EPO stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Normal plasma erythropoietin levels range from 0.01 to 0.03 Units/mL, and can increase up to 100 to 1,000-fold during hypoxia or anemia. Graber and Krantz, *Ann. Rev. Med.* 29:51 (1978); Eschbach and Adamson, *Kidney Intl.* 28:1 (1985). Recombinant human erythropoietin (rHuEpo or epoietin alpha) is commercially available as EPOGEN.RTM. (epoietin alpha, recombinant human erythropoietin) (Amgen Inc., Thousand Oaks, Calif.) and as PROCRIT.RTM. (epoietin alpha, recombinant human erythropoietin) (Ortho Biotech Inc., Raritan, N.J.).

[0009] Another example of an erythroid-associated disorder is erythrocytosis. Erythrocytosis, a disorder of red blood cell overproduction caused by excessive and/or ectopic erythropoietin production, can be caused by cancers, e.g., a renal cell cancer, a hepatocarcinoma, and a central nervous system cancer. Diseases associated with erythrocytosis include polycythemia, e.g., polycythemia vera, secondary polycythemia, and relative polycythemia.

[0010] A hematological disorder as used herein includes disorders involving B-cells which include, but are not limited to precursor B-cell neoplasms, such as lymphoblastic leukemia/lymphoma. Peripheral B-cell neoplasms include, but are not limited to, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cell neoplasms, multiple myeloma, and related entities, lymphoplasmacytic lymphoma (Waldenström macroglobulinemia), mantle cell lymphoma, marginal zone lymphoma (MAL.Toma), and hairy cell leukemia.

[0011] A hematological disorder as used herein includes disorders of the bone marrow which include but are not limited to: diseases involving hematopoietic stem cells; committed lymphoid progenitor cells; lymphoid cells including B and T-cells; committed myeloid progenitors, including monocytes, granulocytes, and megakaryocytes; and



committed erythroid progenitors. These include but are not limited to the leukemias, including B-lymphoid leukemias, T-lymphoid leukemias, undifferentiated leukemias; erythroleukemia, megakaryoblastic leukemia, monocytic; [leukemias are encompassed with and without differentiation; chronic and acute lymphoblastic leukemia, chronic and acute lymphocytic leukemia, chronic and acute myelogenous leukemia, lymphoma, myelo dysplastic syndrome, chronic and acute myeloid leukemia, myelomonocytic leukemia; chronic and acute myeloblastic leukemia, chronic and acute myelogenous leukemia, chronic and acute promyelocytic leukemia, chronic and acute myelocytic leukemia, hematologic malignancies of monocyte-macrophage lineage, such as juvenile chronic myelogenous leukemia; secondary AML, antecedent hematological disorder; refractory anemia; aplastic anemia; reactive cutaneous angioendotheliomatosis; fibrosing disorders involving altered expression in dendritic cells, disorders including systemic sclerosis, E-M syndrome, epidemic toxic oil syndrome, eosinophilic fasciitis localized forms of scleroderma, keloid, and fibrosing colonopathy; angiomatoid malignant fibrous histiocytoma; carcinoma, including primary head and neck squamous cell carcinoma; sarcoma, including kaposi's sarcoma; fibroadenoma and phyllodes tumors, including mammary fibroadenoma; stromal tumors; phyllodes tumors, including histiocytoma; erythroblastosis; neurofibromatosis; diseases of the vascular endothelium; demyelinating, particularly in old lesions; gliosis, vasogenic edema, vascular disease, Alzheimer's and Parkinson's disease; T-cell lymphomas; B-cell lymphomas.

[0012] A hematological disorder as used herein can include platelet disorders including but not limited to disorders related to reduced platelet number, thrombocytopenia, include idiopathic thrombocytopenic purpura, including acute idiopathic thrombocytopenic purpura, drug-induced thrombocytopenia, HIV-associated thrombocytopenia, and thrombotic microangiopathies: thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome.

[0013] A hematological disorder can also include thrombosis. Thrombosis can result from platelet dysfunction, e.g. seen in myocardial infarction, angina, hypertension, lipid disorders, diabetes mellitus; myelodysplastic syndromes; myeloproliferative syndromes (including polycythemia vera and thrombocythemia); thrombotic thrombocytopenic purpuras; HIV-induced platelet disorders (AIDS-Thrombocytopenia); heparin induced thrombocytopenia; mural cell alterations/interactions leading to platelet aggregation/degranulation, vascular endothelial cell activation/injury, monocyte/macrophage extravasation and smooth muscle cell proliferation; autoimmune disorders such as, but not limited to vasculitis, antiphospholipid syndromes, systemic lupus

erythromatosis; inflammatory diseases, such as, but not limited to immune activation; graft Vs host disease; radiation induced hypercoagulation; clotting factor dysregulation either hereditary (autosomal dominant or recessive) such as, but not limited to clotting factor pathways including protein C/S, Anti-thrombin III deficiency, and the Factor V Leiden mutation or acquired such as but not limited to autoimmune, cancer -associated and drug-induced dysregulation of clotting factors.

**[0014]** A hematological disorder as used herein can include red cell disorders including but not limited to, anemias, such as hemolytic anemias, including hereditary spherocytosis, hemolytic disease due to erythrocyte enzyme defects: glucose-6-phosphate dehydrogenase deficiency, sickle cell disease, thalassemia syndromes, paroxysmal nocturnal hemoglobinuria, immunohemolytic anemia, and hemolytic anemia resulting from trauma to red cells; and anemias of diminished erythropoiesis, including megaloblastic anemias, such as anemias of vitamin B12 deficiency: pernicious anemia, and anemia of folate deficiency, iron deficiency anemia, anemia of chronic disease, aplastic anemia, pure red cell aplasia, and other forms of marrow failure.

**[0015]** A hematological disorder as used herein can include disease of T cells including but not limited to, cell-mediated hypersensitivity, such as delayed type hypersensitivity and T-cell-mediated cytotoxicity, and transplant rejection; autoimmune diseases, such as systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, inflammatory myopathies, mixed connective tissue disease, and polyarteritis nodosa and other vasculitides; immunologic deficiency syndromes, including but not limited to, primary immunodeficiencies, such as thymic hypoplasia, severe combined immunodeficiency diseases, and AIDS; leukopenia; reactive (inflammatory) proliferations of white cells, including but not limited to, leukocytosis, acute nonspecific lymphadenitis, and chronic nonspecific lymphadenitis; neoplastic proliferations of white cells, including but not limited to lymphoid neoplasms, such as precursor T-cell neoplasms, such as acute lymphoblastic leukemia/lymphoma, peripheral T-cell and natural killer cell neoplasms that include peripheral T-cell lymphoma, unspecified, adult T-cell leukemia/lymphoma, mycosis fungoides and Sézary syndrome, and Hodgkin disease.

**[0016]** A hematological cell can include, but is not limited to a bone marrow cell, a hematopoietic stem cell, an erythroid cell including a red blood cell, lymphoid cells including a B- and a T-cell, a myeloid (neutrophil) cell including a monocyte, a granulocyte, and a megakaryocyte, and a platelet.

[0017] One aspect of the invention features 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides and biologically active or antigenic fragments thereof that are useful, e.g., as reagents or targets in assays applicable to treatment and diagnosis of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mediated or related disorders, e.g., hematopoietic disorders (e.g., erythroid associated disorders). In another embodiment, the invention provides 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides having a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity.

[0018] In a related aspect, the invention provides 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides or fragments operatively linked to non-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides to form fusion proteins.

[0019] In another aspect, the invention features antibodies and antigen-binding fragments thereof, that react with, or more preferably, specifically bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides.

[0020] In another aspect, the invention provides methods of screening for compounds that modulate the expression or activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417,

57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides or nucleic acids.

**[0021]** In still another aspect, the invention provides a process for modulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide or nucleic acid expression or activity, e.g. using the screened compounds. In certain embodiments, the methods involve treatment of conditions related to decreased activity or expression of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptides or nucleic acids, such as conditions involving aberrant cellular proliferation of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, e.g., a hematopoietic cell (e.g., a myeloid (neutrophil) cell, a monocyte, an erythroid cell, a bone marrow cell, a CD34-expressing cell, a megakaryocyte). The condition may involve increased hematopoietic cell activity or proliferation as in the case of leukemia, e.g., an erythroleukemia; or decreased hematopoietic cell differentiation as in the case of, e.g., an anemia.

**[0022]** In still another aspect, the invention features a method of modulating (e.g., enhancing or inhibiting) the proliferation, survival, and/or differentiation of a cell, e.g., a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, e.g., a hematopoietic cell (e.g., a myeloid (neutrophil) cell, a monocyte, an erythroid cell, a bone marrow cell, a CD34-expressing cell, a megakaryocyte). The method includes contacting the cell with an agent that modulates the activity or expression of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661,

16052, 1521, 6662, 13913, 12405 or 5014 polypeptide or nucleic acid, in an amount effective to modulate the proliferation and/or differentiation of the cell.

**[0023]** In a preferred embodiment, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide has an amino acid sequence identical to, or substantially identical to, SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80. In other embodiments, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide is a fragment of at least 15, 20, 50, 100, 150, 180, 200, or more contiguous amino acids of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80.

**[0024]** In a preferred embodiment, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid has a nucleotide sequence identical to, or substantially identical to, SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79. In other embodiments, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid is a fragment of at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, or more contiguous nucleotides of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79.

**[0025]** In a preferred embodiment, an agent modulates (e.g., increases or decreases) expression of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661,

16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid by, e.g., modulating transcription, mRNA stability, etc.

[0026] In preferred embodiments, the agent is a peptide, a phosphopeptide, a small molecule, e.g., a member of a combinatorial library, or an antibody, or any combination thereof. The antibody can be conjugated to a therapeutic moiety selected from the group consisting of a cytotoxin, a cytotoxic agent and a radioactive metal ion.

[0027] In additional preferred embodiments, the agent is an antisense, a ribozyme, or a triple helix molecule, or a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid, or any combination thereof.

[0028] In a preferred embodiment, the agent is administered in combination with a cytotoxic agent.

[0029] In a preferred embodiment, the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, is a hematopoietic cell, e.g., a myeloid, lymphoid or erythroid cell, or a precursor cell thereof. Examples of such cells include myelocytic cells (polymorphoneuclear cells), erythrocytic cells, lymphocytes, monocytes, reticular cells, plasma cells and megakaryocytes, as well as stem cells for the different lineages, and precursors for the committed progenitor cells, for example, precursors of red blood cells (erythroblasts), macrophages (monoblasts), platelets (megakaryocytes), polymorphoneuclear leucocytes (myeloblasts), and lymphocytes (lymphoblasts).

[0030] In a preferred embodiment, the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, is a bone marrow cell, e.g., a bone marrow CD34-expressing cell. Examples of CD34-expressing cells include immature haematopoietic precursor cells, haematopoietic colony-forming cells in bone marrow, including unipotent (CFU-GM, BFU-E) and pluripotent progenitors (CFU-GEMM, CFU-Mix and CFU-blast); as well as stromal cell precursors, terminal deoxynucleotidyl transferase (TdT) expressing B- and T-lymphoid precursors, early myeloid cells and early erythroid cells.

[0031] In a preferred embodiment, the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, is a bone marrow erythroid cell, e.g., an erythroid progenitor (e.g., a glycophorin A (GPA) (low)CD71+ cell) or a differentiated cell, e.g., an erythrocyte or a megakaryocyte.

[0032] In a preferred embodiment, the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, is further contacted with a protein, e.g., a cytokine. Preferably, the protein is selected from the group consisting of G-CSF, GM-CSF, stem cell factor, and preferably erythropoietin. The protein contacting step can occur before, at the same time, or after the agent is contacted. The protein contacting step can be effected *in vitro* or *ex vivo*. For example, the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell is obtained from a subject, e.g., a patient, and contacted with the protein *ex vivo*. The treated cell can be re-introduced into the subject. Alternatively, the protein contacting step can occur *in vivo*.

[0033] In a preferred embodiment, the agent and the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-polypeptide or nucleic acid are contacted *in vitro* or *ex vivo*.

[0034] In a preferred embodiment, the contacting step is effected *in vivo* in a subject, e.g., as part of a therapeutic or prophylactic protocol. Preferably, the subject is a human, e.g., a patient with a hematopoietic disorder, e.g., a leukemia or an erythroid-associated disorder. For example, the subject can be a patient with an anemia, e.g., hemolytic anemia, aberrant erythropoiesis, secondary anemia in non-hematologic disorders, anemia of chronic disease such as chronic renal failure; endocrine deficiency disease; and/or erythrocytosis (e.g., polycythemia). Alternatively, the subject can be a cancer patient, e.g., a patient with leukemic cancer, e.g., an erythroid leukemia, or a carcinoma,

e.g., a renal carcinoma. In other embodiments, the subject is a non-human animal, e.g., an experimental animal.

**[0035]** The contacting step(s) can be repeated.

**[0036]** In a preferred embodiment, the agent decreases the proliferation and/or enhances the differentiation of the cell, e.g., the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, e.g., the hematopoietic cell (e.g., the myeloid (neutrophil) cell, the monocyte, the erythroid cell, the bone marrow cell, the CD34-expressing cell, the megakaryocyte). Such agents can be used to treat or prevent cancers, e.g., leukemic cancers.

**[0037]** In a preferred embodiment, the agent increases the number of hematopoietic cells (e.g., myeloid (neutrophil) cells, monocytes, erythroid cells, bone marrow cells, CD34-expressing cells, megakaryocytes), by e.g., increasing the proliferation, survival, and/or stimulating the differentiation, of progenitor cells. Such agents can be used to treat or prevent hematopoietic disorders, e.g., anemias (e.g., hemolytic anemias, aberrant erythropoiesis, secondary anemias in nonhematologic disorders, anemias of chronic diseases such as chronic renal failure; endocrine deficiency diseases; and/or erythrocytosis, e.g., polycythemias).

**[0038]** In another aspect, the invention features a method of modulating hematopoiesis, e.g., erythropoiesis, comprising contacting a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-expressing cell, e.g., a hematopoietic cell, (e.g., a myeloid (neutrophil) cell, a monocyte, an erythroid cell, a bone marrow cell, a CD34-expressing cell, a megakaryocyte), with a agent that increases or decreases the activity or expression of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide or nucleic acid, thereby modulating the differentiation of the hematopoietic cell.

**[0039]** In yet another aspect, the invention features a method of treating or preventing a hematopoietic disorder, e.g., an erythroid-associated disorder, in a subject. The method includes administering to the subject an effective amount of a agent that



modulates the activity or expression of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide or nucleic acid such that the hematopoietic disorder is ameliorated or at least one symptom of the hematological disorder is decreased.

### **Molecules of the Present Invention**

#### **Gene ID 9118**

[0040] The human 9118 sequence (SEQ ID NO:1), known also as chlordecone reductase homolog, is approximately 1175 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 11 to 982 of SEQ ID NO:1, encodes a 323 amino acid protein (SEQ ID NO:2).

[0041] As assessed by TaqMan analysis, 9118 mRNA was expressed at high levels in CD34 progenitor cells, pooled erythroid cells and GPA high cells. Further TaqMan experiments indicated that 9118 mRNA was also expressed in liver, kidney, lung, spleen and fetal liver tissue samples. Within hematopoietic samples, 9118 mRNA expression was highest in erythroid cells followed by macrophages and progenitor cells.

[0042] 9118 potentially plays a role in erythroid cell differentiation and proliferation. Therefore, inhibition of 9118 function would lead to increased proliferation with differentiation of erythroid cells from CFU-E to mature erythroid cells.

[0043] Due to the expression pattern of 9118 mRNA in CD34 progenitors, pooled erythroid cells and GPA high cells, along with its functional role, 9118 may play a role in regulating diseases associated with hematological disorders. Therefore, modulators of 9118 activity would be useful in treating hematological disorders. 9118 polypeptides of the current invention would be useful to screen for modulators of 9118 activity.

#### **Gene ID 990**

[0044] The human 990 sequence (SEQ ID NO:3), known also as tripeptidyl peptidase II, is approximately 4626 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 24 to 3773 of SEQ ID NO:3, encodes a 1249 amino acid protein (SEQ ID NO:4).

[00171] The human 53003 sequence (SEQ ID NO:61), known also as acyl-CoA synthetase MACS1, is approximately 2074 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 79 to 1812 of SEQ ID NO:61, encodes a 577 amino acid protein (SEQ ID NO:62).

[00172] As assessed by TaqMan analysis, 53003 mRNA expression was very restricted, detectable only in erythroid cells, ovary and pancreas. 53003 mRNA expression in hematopoietic cells was very restricted to Day 10 pooled differentiating erythroid cells. 53003 mRNA expression was also detected in CD34+ progenitors. During erythroid differentiation, 53003 mRNA expression was strongly up regulated at day 6 in a manner that very closely resembles EPO receptor expression. It was also down regulated in GPA low cells when compared to GPA high cells. Furthermore, 53003 mRNA expression was increased in BFU-E cultures with EPO compared to those without EPO.

[00173] Expression of the 53003 mouse ortholog was detectable in mouse hematopoietic cells, particularly in lineage negative progenitors.

[00174] 53003 is a medium chain acyl-CoA synthetase, also called butyryl-CoA synthetase, which acts on acids from C4 to C11 and on the corresponding 3-hydroxy- and 2,3- or 3,4-unsaturated acids with preference for octanoate as its substrate (*J Biol Chem.* 2001 Sep 21; 276(38):35961-6. Epub 2001 Jul 24). The substrates of MACS1 would lead to differentiation of erythroid cells and its inhibition would lead to increased proliferation of CFU-Es and generation of more erythroid cells.

[00175] Due to 53003 mRNA expression in erythroid cells, along with its functional role, modulators of 53003 would be useful in the treatment of hematological disorders. 53003 polypeptides of the present invention would be useful in screening for modulators of 53003 activity.

#### **Gene ID 965**

[00176] The human 965 sequence (SEQ ID NO:63), known also as protein-tyrosine phosphatase delta (R-PTP-delta), is approximately 6263 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acids 154 to 5892 of SEQ ID NO:63, encodes a 1912 amino acid protein (SEQ ID NO:64).

[00177] As determined by TaqMan analysis, 965 mRNA was expressed at the highest levels in brain and expressed at low levels in most tissues and organs. In hematopoietic cells, 965 mRNA was expressed at the highest levels in CD34 progenitor cells, but not in differentiated hematopoietic cells. In cultures differentiated to myeloid

cells, erythroid cells and megakaryocytes, 965 mRNA expression decreases after 24 and 48 hours in culture, indicating that its key role is in CD34 progenitor cells.

[00178] Expression of the mouse ortholog of 965 was detected in lineage negative fractions of the bone marrow corresponding to the progenitor cell population. It was also detected in bone marrow white blood cells, TER119+ erythroid cells and in Gr-1+ neutrophils.

[00179] PTP-delta is selectively decreased in primary hepatomas and hepatoma cell lines, suggesting that it is a tumor suppressor. Inhibition of PTP-delta function with an inhibitor would lead to increased proliferation of CD34 progenitor cells and a subsequent increase in erythropoiesis, myelopoiesis and megakaryopoiesis.

[00180] Due to 965 mRNA expression, along with its functional role, modulators of 965 would be useful in the treatment of hematological disorders. 965 polypeptides of the present invention would be useful in screening for modulators of 965 activity.

#### **Gene ID 56639**

[00181] The human 56639 sequence (SEQ ID NO:65), known also as proprotein convertase 4 (PC4), is approximately 2669 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acids 61 to 2328 of SEQ ID NO:65, encodes a 755 amino acid protein (SEQ ID NO:66).

[00182] As assessed by TaqMan analysis, 56639 mRNA was expressed at the highest levels in erythroid cells, brain, pituitary gland and kidney. In hematopoietic cells, 56639 mRNA was expressed at very high levels in pooled Day 10 differentiating erythroid cells, in K562 (erythroleukemia cell line) and in CD34 cells. In erythroid cells, 56639 mRNA expression increased in BFU-E cultures in the presence of EPO. 56639 mRNA expression was detected in GPA low cells at higher levels than in GPA high samples. Low expression of 56639 mRNA was detected in megakaryocytic and neutrophil cultures.

[00183] Expression of the mouse ortholog of 56639 was detected in lineage negative fractions of the bone marrow corresponding to the progenitor cell population.

[00184] Proprotein convertases are calcium-dependent serine proteases related to bacterial subtilisins and to yeast kexin. These enzymes process precursor proteins to their active forms by selective cleavage of the polypeptide at sites following paired basic amino acids. In mammals, this family comprises PC1, PC2, PC4, PC5, furin (FUR), and PACE4. Substrates for these enzymes range from prohormones to precursors for growth factors to cell surface receptors and viral surface glycoproteins. This enzyme is highly expressed in

including untranslated regions. The coding sequence, located at about nucleic acid 358 to 1506 of SEQ ID NO:79, encodes a 382 amino acid protein (SEQ ID NO:80).

[00217] As assessed by TaqMan analysis, 5014 mRNA expression was mainly restricted to hematopoietic cells, being at the highest levels in *in vitro* differentiated Day 10 erythroid cultures. Lower levels of expression were observed in skeletal muscle and in brain samples. 5014 mRNA was also expressed in the erythroid cell line K562, in GPA low erythroid cells and in fetal liver. It was expressed at lower levels in CD34+ progenitor cells and it was detectable in T-cells (CD3+) and B-cells (CD19+). Additional TaqMan analyses using an erythroid panel, demonstrated that 5014 mRNA expression increased significantly with erythroid differentiation *in vitro*. 5014 mRNA expression increased from 24 hours in culture onwards, and expression also increased in BFU-E cultures in the presence of EPO. 5014 mRNA expression was observed in both GPA low erythroid cells and in GPA high expressing cells.

[00218] The mouse ortholog of 5014 showed expression in lineage negative cells and TER119 + cells corresponding to the erythroid progenitors and mature cells. It was also expressed in mononuclear cells and GR1+ive neutrophils.

[00219] 5014 is also known as protein phosphatase 2C alpha isoform (PP2Calpha). PP2C has been described as a negative regulator of MAPK kinase signaling (*J. Biol. Chem.* 2003 May 23;278(21):18945-52. Epub 2003 Mar 19; and *EMBO J.* 1998 Aug 17;17(16):4744-52). The alpha isoform of PP2C has been described in p53 activation (*J. Biol. Chem.* 2003 Apr 18;278(16):14299-305. Epub 2003 Jan 03). p53 deficient cells have an increased proliferative potential compared to wild type controls (*Exp Biol Med* (Maywood). 2002 Jul;227(7):474-9). Therefore, PP2C phosphatases appear to have a role in regulation of proliferation. PP2Calpha may also have a role in the negative regulation of proliferative signaling. Inhibition of PP2Cgamma may therefore lead to increased proliferation of erythroid progenitor cells.

[00220] Due to 5014 mRNA expression in erythroid cells, along with its functional role, modulators of 5014 would be useful in the treatment of hematological disorders. 5014 polypeptides of the present invention would be useful in screening for modulators of 5014 activity.

[00221] Various aspects of the invention are described in further detail in the following subsections:

### I. Screening Assays:

[00222] The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules (organic or inorganic) or other drugs) which bind to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins, have a stimulatory or inhibitory effect on, for example, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate. Compounds identified using the assays described herein may be useful for treating hematological disorders.

[00223] These assays are designed to identify compounds that bind to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, bind to other intracellular or extracellular proteins that interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, and interfere with the interaction of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein with other intercellular or extracellular proteins. For example, in the case of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544,

7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, which is a transmembrane receptor-type protein, such techniques can identify ligands for such a receptor. A 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein ligand or substrate can, for example, be used to at least one symptom of a hematological disorder. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic compounds. Such compounds may also include other cellular proteins.

**[00224]** Compounds identified via assays such as those described herein may be useful, for example, for treating hematological disorders. In instances whereby a hematological disorder condition results from an overall lower level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression and/or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein in a cell or tissue, compounds that interact with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein may include compounds which accentuate or amplify the activity of the bound 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Such compounds would bring about an effective increase in the level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein activity, thus ameliorating symptoms.

**[00225]** In other instances, mutations within the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417,

57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene may cause aberrant types or excessive amounts of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins to be made which have a deleterious effect that leads to a hematological disorder. Similarly, physiological conditions may cause an excessive increase in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression leading hematological disorders. In such cases, compounds that bind to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein may be identified that inhibit the activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Assays for testing the effectiveness of compounds identified by techniques such as those described in this section are discussed herein.

[00226] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially

addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

[00227] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

[00228] Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

[00229] In one embodiment, an assay is a cell-based assay in which a cell which expresses a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is determined. Determining the ability of the test compound to modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity can be accomplished by monitoring, for example, intracellular calcium, IP<sub>3</sub>, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell



proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with hematopoiesis, or the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 - regulated transcription factor. The cell can be of mammalian origin, *e.g.*, a neural cell. In one embodiment, compounds that interact with a receptor domain can be screened for their ability to function as ligands, *i.e.*, to bind to the receptor and modulate a signal transduction pathway. Identification of ligands, and measuring the activity of the ligand-receptor complex, leads to the identification of modulators (*e.g.*, antagonists) of this interaction. Such modulators may be useful in the treatment of hematological disorders.

[00230] The ability of the test compound to modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding to a substrate or to bind to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can also be determined. Determining the ability of the test compound to modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding to a substrate can be accomplished, for example, by coupling the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate with a radioisotope or enzymatic label such that binding of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be determined by

detecting the labeled 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate in a complex. 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 could also be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate in a complex. Determining the ability of the test compound to bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be determined by detecting the labeled 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 compound in a complex. For example, compounds (*e.g.*, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 ligands or substrates) can be labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Compounds can further be

enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

**[00231]** It is also within the scope of this invention to determine the ability of a compound (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 ligand or substrate) to interact with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 without the labeling of either the compound or the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 (McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014.

**[00232]** In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824,

28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate) with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule. Determining the ability of the test compound to modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule can be accomplished, for example, by determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to bind to or interact with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule.

[00233] Determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or a biologically active fragment thereof, to bind to or interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to bind to or interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662,

13913, 12405 or 5014 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular  $\text{Ca}^{2+}$ , diacylglycerol,  $\text{IP}_3$ , cAMP), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response (*e.g.*, gene expression).

[00234] In yet another embodiment, an assay of the present invention is a cell-free assay in which a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to bind to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof is determined. Preferred biologically active portions of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins to be used in assays of the present invention include fragments which participate in interactions with non- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 molecules, *e.g.*, fragments with high surface probability scores. Binding of the test compound to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003,

965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof with a known compound which binds 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, wherein determining the ability of the test compound to interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein comprises determining the ability of the test compound to preferentially bind to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 or biologically active portion thereof as compared to the known compound. Compounds that modulate the interaction of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 with a known target protein may be useful in regulating the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, especially a mutant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.

**[00235]** In another embodiment, the assay is a cell-free assay in which a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014

protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be accomplished, for example, by determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to bind to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule by one of the methods described above for determining direct binding. Determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to bind to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[00236] In another embodiment, determining the ability of the test compound to modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620,

21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be accomplished by determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to further modulate the activity of a downstream effector of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

[00237] In yet another embodiment, the cell-free assay involves contacting a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or biologically active portion thereof with a known compound which binds the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, wherein determining the ability of the test compound to interact with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein comprises determining the ability of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to preferentially bind



to or modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule.

[00238] In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, or interaction of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/ 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following

incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding or activity determined using standard techniques.

[00239] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or target molecules but which do not interfere with binding of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584,

27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or target molecule.

**[00240]** In another embodiment, modulators of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein in the cell is determined. The level of expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein in the presence of the candidate compound is compared to the level of expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression based on this comparison. For example, when expression of 9118,

990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein expression. Alternatively, when expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein expression. The level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein expression in the cells can be determined by methods described herein for detecting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or protein.

[00241] In yet another aspect of the invention, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to

or interact with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 (" 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-binding proteins" or " 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-bp") and are involved in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Such 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-binding proteins are also likely to be involved in the propagation of signals by the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 targets as, for example, downstream elements of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-mediated signaling pathway. Alternatively, such 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-binding proteins are likely to be 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584,

27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 inhibitors.

[00242] The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.

[00243] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be confirmed *in vivo*, *e.g.*, in an animal such as an animal model for hematological disorders, as described herein.

[00244] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulating agent, an antisense 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecule, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-specific antibody, or a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[00245] Any of the compounds, including but not limited to compounds such as those identified in the foregoing assay systems, may be tested for the ability to treat hematological disorders. Cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to at least one symptom of hematological disorders are described herein.

[00246] In addition, animal-based models of hematological disorders, such as those described herein, may be used to identify compounds capable of treating hematological disorders. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies, and interventions which may be effective in treating hematological disorders. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to treat hematological disorders, at a sufficient concentration and for a time sufficient to elicit such an amelioration of hematological

disorders in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of the symptoms of hematological disorders before and after treatment.

**[00247]** With regard to intervention, any treatments which reverse any aspect of hematological disorders should be considered as candidates for human hematological disorders therapeutic intervention. Dosages of test agents may be determined by deriving dose-response curves.

**[00248]** Additionally, gene expression patterns may be utilized to assess the ability of a compound to at least one symptom of hematological disorders. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR. In one embodiment, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences may be used as probes and/or PCR primers for the generation and corroboration of such gene expression profiles.

**[00249]** Gene expression profiles may be characterized for known states, either hematological disease or normal, within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

**[00250]** For example, administration of a compound may cause the gene expression profile of a hematological disorder disease model system to more closely resemble the control system. Administration of a compound may, alternatively, cause the gene expression profile of a control system to begin to mimic hematological disorders or a hematological disorder disease state. Such a compound may, for example, be used in further characterizing the compound of interest, or may be used in the generation of additional animal models.



## II. Cell- and Animal-Based Model Systems

[00251] Described herein are cell- and animal-based systems which act as models for hematological disorders. These systems may be used in a variety of applications. For example, the cell- and animal-based model systems may be used to further characterize differentially expressed genes associated with hematological disease, *e.g.*, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. In addition, animal- and cell-based assays may be used as part of screening strategies designed to identify compounds which are capable of ameliorating hematological disorders, as described, below. Thus, the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions which may be effective in treating a hematological disorder. Furthermore, such animal models may be used to determine the LD50 and the ED50 in animal subjects, and such data can be used to determine the *in vivo* efficacy of potential hematological disorders treatments.

### A. Animal-Based Systems

[00252] Animal-based model systems of hematological disorders may include, but are not limited to, non-recombinant and engineered transgenic animals.

[00253] Non-recombinant animal models for hematological disorders may include, for example, genetic models.

[00254] Additionally, animal models exhibiting hematological disorders may be engineered by using, for example, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences described above, in conjunction with techniques for producing transgenic animals that are well known to those of skill in the art. For example, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences may be introduced into, and overexpressed in, the genome of the animal of interest, or, if endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584,

27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences are present, they may either be overexpressed or, alternatively, be disrupted in order to underexpress or inactivate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression.

**[00255]** The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences have been introduced into their genome or homologous recombinant animals in which endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences have been altered. Such animals are useful for studying the function and/or activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 and for identifying and/or evaluating modulators of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a

transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

[00256] A transgenic animal used in the methods of the invention can be created by introducing a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 cDNA sequence can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, such as a mouse or rat 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, can be used as a transgene. Alternatively, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene homologue, such as another 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600,

25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 family member, can be isolated based on hybridization to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 cDNA sequences and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 transgene to direct expression of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 transgene in its genome and/or expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003,

965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can further be bred to other transgenic animals carrying other transgenes.

**[00257]** To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. The 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene can be a human gene but more preferably, is a non-human homologue of a human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. For example, a rat 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene can be used to construct a homologous recombination nucleic acid molecule, *e.g.*, a vector, suitable for altering an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene in the mouse genome. In a preferred embodiment, the homologous recombination nucleic acid molecule is designed such that, upon homologous recombination, the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the homologous recombination nucleic acid molecule can be designed such

that, upon homologous recombination, the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein). In the homologous recombination nucleic acid molecule, the altered portion of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene to allow for homologous recombination to occur between the exogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene carried by the homologous recombination nucleic acid molecule and an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene in a cell, *e.g.*, an embryonic stem cell. The additional flanking 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the homologous recombination nucleic acid molecule (see, *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The homologous recombination nucleic acid molecule is

introduced into a cell, *e.g.*, an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene has homologously recombined with the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells can then be injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination nucleic acid molecules, *e.g.*, vectors, or homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

[00258] In another embodiment, transgenic non-human animals for use in the methods of the invention can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

**[00259]** Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G<sub>0</sub> phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

**[00260]** The 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 transgenic animals that express 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 peptide (detected immunocytochemically, using antibodies directed against 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 epitopes) at easily detectable levels should then be further evaluated to identify those animals which display characteristic hematological disorders.

#### B. Cell-Based Systems

**[00261]** Cells that contain and express 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences which encode a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600,



25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, and, further, exhibit cellular phenotypes associated with e.g. hematopoiesis, may be used to identify compounds that exhibit an effect. Such cells may include non-recombinant monocyte cell lines, such as U937 (ATCC# CRL-1593), THP-1 (ATCC# TIB-202), and P388D1 (ATCC# TIB-63); endothelial cells such as human umbilical vein endothelial cells (HUVECs), human microvascular endothelial cells (HMVEC), and bovine aortic endothelial cells (BAECs); as well as generic mammalian cell lines such as HeLa cells and COS cells, e.g., COS-7 (ATCC# CRL-1651), cells described supra which constitute those cells relevant to hematology. Further, such cells may include recombinant, transgenic cell lines. For example, the hematological disorders animal models of the invention, discussed above, may be used to generate cell lines, containing one or more cell types involved in e.g. hematopoiesis, that can be used as cell culture models for this disorder. While primary cultures derived from the hematological disorders model transgenic animals of the invention may be utilized, the generation of continuous cell lines is preferred. For examples of techniques which may be used to derive a continuous cell line from the transgenic animals, see Small *et al.*, (1985) *Mol. Cell Biol.* 5:642-648.

**[00262]** Alternatively, cells of a cell type known to be involved in e.g. hematopoiesis may be transfected with sequences capable of increasing or decreasing the amount of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression within the cell. For example, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences may be introduced into, and overexpressed in, the genome of the cell of interest, or, if endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences are present, they may be either overexpressed or, alternatively disrupted in order to underexpress or inactivate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584,

27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression.

[00263] In order to overexpress a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, the coding portion of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene may be ligated to a regulatory sequence which is capable of driving gene expression in the cell type of interest, *e.g.*, an endothelial cell. Such regulatory regions will be well known to those of skill in the art, and may be utilized in the absence of undue experimentation. Recombinant methods for expressing target genes are described above.

[00264] For underexpression of an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequence, such a sequence may be isolated and engineered such that when reintroduced into the genome of the cell type of interest, the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 alleles will be inactivated. Preferably, the engineered 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence is introduced via gene targeting such that the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence is disrupted upon integration of the engineered 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence into the cell's genome. Transfection of host cells with

9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 genes is discussed, above.

**[00265]** Cells treated with compounds or transfected with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 genes can be examined for phenotypes associated with e.g. hematopoiesis.

**[00266]** Transfection of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid may be accomplished by using standard techniques (described in, for example, Ausubel (1989) *supra*). Transfected cells should be evaluated for the presence of the recombinant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences, for expression and accumulation of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA, and for the presence of recombinant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein production. In instances wherein a decrease in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression is desired, standard techniques may be used to demonstrate whether a decrease in endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression and/or in 9118, 990, 17662, 81982, 630, 21472,

17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein production is achieved.

**[00267]** Also provided are cells or a purified preparation thereof, e.g., human cells, in which an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is under the control of a regulatory sequence that does not normally control the expression of the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. The expression characteristics of an endogenous gene within a cell, e.g., a cell line or microorganism, can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. For example, an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, e.g., a gene which is "transcriptionally silent," e.g., not normally expressed, or expressed only at very low levels, may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombinations, can be used to insert the heterologous DNA as described in, e.g., Chappel, US 5,272,071; WO 91/06667, published on May 16, 1991.

### III. Predictive Medicine:

**[00268]** The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for

determining 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein and/or nucleic acid expression as well as 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity, in the context of a biological sample (*e.g.*, blood, serum, cells, *e.g.*, endothelial cells, or tissue, *e.g.*, vascular tissue) to thereby determine whether an individual is afflicted with a predisposition or is experiencing hematological disorders. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a hematological disorder. For example, mutations in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene can be assayed for in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a hematological disorder.

[00269] Another aspect of the invention pertains to monitoring the influence of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulators (*e.g.*, anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 ribozymes) on the expression or activity of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 in clinical trials.

[00270] These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

[00271] To determine whether a subject is afflicted with a disease, a biological sample may be obtained from a subject and the biological sample may be contacted with a compound or an agent capable of detecting a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or nucleic acid (*e.g.*, mRNA or genomic DNA) that encodes a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, in the biological sample. A preferred agent for detecting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA or genomic DNA. The nucleic acid probe can be, for example, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid set forth in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 35, 40, 45, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014

mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

[00272] A preferred agent for detecting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein in a sample is an antibody capable of binding to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')<sub>2</sub>) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

[00273] The term "biological sample" is intended to include tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present within a subject. That is, the detection method of the invention can be used to detect 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein include enzyme linked immunosorbent assays (ELISAs), Western blots,

immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein include introducing into a subject a labeled anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[00274] In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA, or genomic DNA, such that the presence of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA or genomic DNA in the control sample with the presence of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA or genomic DNA in the test sample.



**B. Prognostic Assays**

**[00275]** The present invention further pertains to methods for identifying subjects having or at risk of developing a disease associated with aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity.

**[00276]** As used herein, the term "aberrant" includes a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity which deviates from the wild type 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does not follow the wild type developmental pattern of expression or the subcellular pattern of expression. For example, aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity is intended to include the cases in which a mutation in the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene causes the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene to be under-expressed or over-expressed and situations in which such mutations result in a non-functional 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or a protein which does not function in a wild-type fashion, *e.g.*, a protein which does not

interact with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate, or one which interacts with a non- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate.

**[00277]** The assays described herein, such as the preceding diagnostic assays or the following assays, can be used to identify a subject having or at risk of developing a disease. A biological sample may be obtained from a subject and tested for the presence or absence of a genetic alteration. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 2) an addition of one or more nucleotides to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 3) a substitution of one or more nucleotides of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 4) a chromosomal rearrangement of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 5) an alteration in the level of a messenger RNA transcript of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 6) aberrant modification of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661,

16052, 1521, 6662, 13913, 12405 or 5014 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, 8) a non-wild type level of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-protein, 9) allelic loss of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, and 10) inappropriate post-translational modification of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-protein.

[00278] As described herein, there are a large number of assays known in the art which can be used for detecting genetic alterations in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. For example, a genetic alteration in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene may be detected using a probe/primer in a polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene (see Abravaya *et al.* (1995) *Nucleic Acids*

*Res.* 23:675-682). This method includes collecting a biological sample from a subject, isolating nucleic acid (*e.g.*, genomic DNA, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene under conditions such that hybridization and amplification of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[00279] Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

[00280] In an alternative embodiment, mutations in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene from a biological sample can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

[00281] In other embodiments, genetic mutations in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be identified by hybridizing biological sample derived and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7:244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al.* (1996) *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential, overlapping probes. This step allows for the identification of point mutations. This step is followed by a second hybridization array that allows for the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

[00282] In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene in a biological sample and detect mutations by comparing the sequence of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 in the biological sample with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert (1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger (1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeye, C. W. (1995) *Biotechniques* 19:448-53),

including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

[00283] Other methods for detecting mutations in the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397 and Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

[00284] In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from

HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence, *e.g.*, a wild-type 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

[00285] In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144 and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

[00286] In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing

gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to ensure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

[00287] Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

[00288] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

[00289] Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator (*e.g.*, an agonist,



antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule) to effectively treat a disease.

C. Monitoring of Effects During Clinical Trials

[00290] The present invention further provides methods for determining the effectiveness of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator identified herein) in treating a disease. For example, the effectiveness of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator in increasing 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression, protein levels, or in upregulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity, can be monitored in clinical trials of subjects exhibiting decreased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression, protein levels, or downregulated 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Alternatively, the effectiveness of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052,

1521, 6662, 13913, 12405 or 5014 modulator in decreasing 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression, protein levels, or in downregulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity, can be monitored in clinical trials of subjects exhibiting increased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression, protein levels, or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. In such clinical trials, the expression or activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, and preferably, other genes that have been implicated in e.g. hematopoiesis or thrombosis can be used as a "read out" or marker of the phenotype of a particular cell.

**[00291]** For example, and not by way of limitation, genes, including 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014, that are modulated in cells by treatment with an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity (e.g., identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents which modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity on subjects suffering from

a hematological disorder in, for example, a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 and other genes implicated in the hematological disorders disorder. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods described herein, or by measuring the levels of activity of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. This response state may be determined before, and at various points during treatment of the individual with the agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity.

[00292] In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA, or genomic

DNA in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA, or genomic DNA in the pre-administration sample with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an embodiment, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

#### IV. Methods of Treatment:

[00293] The present invention provides for both prophylactic and therapeutic methods of treating a subject, *e.g.*, a human, at risk of (or susceptible to) a disease. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics. "Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers to the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype").

[00294] Thus, another aspect of the invention provides methods for tailoring an subject's prophylactic or therapeutic treatment with either the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 molecules of the present invention or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

#### A. Prophylactic Methods

[00295] In one aspect, the invention provides a method for preventing in a subject, a disease by administering to the subject an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Subjects at risk for a hematological disorder, can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of a prophylactic agent can occur prior to the

manifestation of symptoms characteristic of aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity, such that a disease is prevented or, alternatively, delayed in its progression. Depending on the type of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 aberrancy, for example, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 agonist or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

#### B. Therapeutic Methods

[00296] Described herein are methods and compositions whereby hematological disorders may be ameliorated. Certain hematological disorders are brought about, at least in part, by an excessive level of a gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of hematological disorders. Techniques for the reduction of gene expression levels or the activity of a protein are discussed below.

[00297] Alternatively, certain other hematological disorders are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a protein's activity. As such, an increase in the level of gene expression and/or the activity of such proteins would bring about the amelioration of hematological disorders.

[00298] In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a gene's expression, or the activity of the gene product, will reinforce the protective

effect it exerts. Some hematological disorders states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of hematological disorders. Techniques for increasing target gene expression levels or target gene product activity levels are discussed herein.

[00299] Accordingly, another aspect of the invention pertains to methods of modulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 or agent that modulates one or more of the activities of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein activity associated with the cell (*e.g.*, an endothelial cell or an ovarian cell). An agent that modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 ligand or substrate), a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody, a 9118, 990, 17662, 81982, 630,

21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 agonist or antagonist, a peptidomimetic of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activities. Examples of such stimulatory agents include active 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein and a nucleic acid molecule encoding 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 that has been introduced into the cell. In another embodiment, the agent inhibits one or more 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activities. Examples of such inhibitory agents include antisense 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules, anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies, and 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 inhibitors. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent)



or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity. In another embodiment, the method involves administering a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity.

[00300] Stimulation of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is desirable in situations in which 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is abnormally downregulated and/or in which increased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is likely to have a beneficial effect. Likewise, inhibition of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259,

21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is desirable in situations in which 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is abnormally upregulated and/or in which decreased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is likely to have a beneficial effect.

(i) Methods for Inhibiting Target Gene Expression, Synthesis, or Activity

[00301] As discussed above, genes involved in hematological disorders may cause such disorders via an increased level of gene activity. In some cases, such up-regulation may have a causative or exacerbating effect on the disease state. A variety of techniques may be used to inhibit the expression, synthesis, or activity of such genes and/or proteins.

[00302] For example, compounds such as those identified through assays described above, which exhibit inhibitory activity, may be used in accordance with the invention to at least one symptom of hematological disorders. Such molecules may include, but are not limited to, small organic molecules, peptides, antibodies, and the like.

[00303] For example, compounds can be administered that compete with endogenous ligand for the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. The resulting reduction in the amount of ligand-bound 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein will modulate endothelial cell physiology. Compounds that can be particularly useful for this purpose include, for example, soluble proteins or peptides, such as peptides comprising one or more of the extracellular domains, or portions and/or analogs thereof, of the 9118, 990, 17662, 81982, 630, 21472, 17692,

19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, including, for example, soluble fusion proteins such as Ig-tailed fusion proteins. (For a discussion of the production of Ig-tailed fusion proteins, see, for example, U.S. Pat. No. 5,116,964).

Alternatively, compounds, such as ligand analogs or antibodies, that bind to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 receptor site, but do not activate the protein, (*e.g.*, receptor-ligand antagonists) can be effective in inhibiting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein activity.

[00304] Further, antisense and ribozyme molecules which inhibit expression of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene may also be used in accordance with the invention to inhibit aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene activity. Still further, triple helix molecules may be utilized in inhibiting aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene activity.

[00305] The antisense nucleic acid molecules used in the methods of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The

hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

[00306] In yet another embodiment, an antisense nucleic acid molecule used in the methods of the invention is an  $\alpha$ -anomeric nucleic acid molecule. An  $\alpha$ -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

[00307] In still another embodiment, an antisense nucleic acid used in the methods of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA transcripts to thereby inhibit translation of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA. A ribozyme having specificity for a 577, 20739 or 57145-encoding

nucleic acid can be designed based upon the nucleotide sequence of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a 577, 20739 or 57145-encoding mRNA (see, for example, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

Alternatively, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, for example, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418).

[00308] 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression can also be inhibited by targeting nucleotide sequences complementary to the regulatory region of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 (*e.g.*, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 promoter and/or enhancers) to form triple helical structures that prevent transcription of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene in target cells (see, for example, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15).

[00309] Antibodies that are both specific for the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein and interfere with its activity may also be used to modulate or inhibit 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein function. Such antibodies may be generated using standard techniques described herein, against the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein itself or against peptides corresponding to portions of the protein. Such antibodies include but are not limited to polyclonal, monoclonal, Fab fragments, single chain antibodies, or chimeric antibodies.

[00310] In instances where the target gene protein is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin liposomes may be used to deliver the antibody or a fragment of the Fab region which binds to the target epitope into cells. Where fragments of the antibody are used, the smallest inhibitory fragment which binds to the target protein's binding domain is preferred. For example, peptides having an amino acid sequence corresponding to the domain of the variable region of the antibody that binds to the target gene protein may be used. Such peptides may be synthesized chemically or produced via recombinant DNA technology using methods well known in the art (described in, for example, Creighton (1983), *supra*; and Sambrook *et al.* (1989) *supra*). Single chain neutralizing antibodies which bind to intracellular target gene epitopes may also be administered. Such single chain antibodies may be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:7889-7893).

[00311] In some instances, the target gene protein is extracellular, or is a transmembrane protein, such as the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661,

16052, 1521, 6662, 13913, 12405 or 5014 protein. Antibodies that are specific for one or more extracellular domains of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, for example, and that interfere with its activity, are particularly useful in treating hematological disorders or a hematological disorder. Such antibodies are especially efficient because they can access the target domains directly from the bloodstream. Any of the administration techniques described below which are appropriate for peptide administration may be utilized to effectively administer inhibitory target gene antibodies to their site of action.

(ii) Methods for Restoring or Enhancing Target Gene Activity

[00312] Genes that cause hematological disorders may be underexpressed within disease situations. Alternatively, the activity of the protein products of such genes may be decreased, leading to the development of hematological disorders. Such down-regulation of gene expression or decrease of protein activity might have a causative or exacerbating effect on the disease state.

[00313] In some cases, genes that are up-regulated in the disease state might be exerting a protective effect. A variety of techniques may be used to increase the expression, synthesis, or activity of genes and/or proteins that exert a protective effect in response to hematological disorders conditions.

[00314] Described in this section are methods whereby the level 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity may be increased to levels wherein hematological disorders are ameliorated. The level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity may be increased, for example, by either increasing the level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600,

25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene expression or by increasing the level of active 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein which is present.

**[00315]** For example, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, at a level sufficient to at least one symptom of hematological disorders may be administered to a patient exhibiting such symptoms. Any of the techniques discussed below may be used for such administration. One of skill in the art will readily know how to determine the concentration of effective, non-toxic doses of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, utilizing techniques such as those described below.

**[00316]** Additionally, RNA sequences encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein may be directly administered to a patient exhibiting hematological disorders, at a concentration sufficient to produce a level of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein such that hematological disorders are ameliorated. Any of the techniques discussed below, which achieve intracellular administration of compounds, such as, for example, liposome administration, may be used for the administration of such RNA molecules. The RNA molecules may be produced, for example, by recombinant techniques such as those described herein.

**[00317]** Further, subjects may be treated by gene replacement therapy. One or more copies of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908,



14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, or a portion thereof, that directs the production of a normal 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 function, may be inserted into cells using vectors which include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes.

Additionally, techniques such as those described above may be used for the introduction of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene sequences into human cells.

[00318] Cells, preferably, autologous cells, containing 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expressing gene sequences may then be introduced or reintroduced into the subject at positions which allow for the amelioration of hematological disorders. Such cell replacement techniques may be preferred, for example, when the gene product is a secreted, extracellular gene product.

### C. Pharmaceutical Compositions

[00319] Another aspect of the invention pertains to methods for treating a subject suffering from a disease. These methods involve administering to a subject an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity (e.g., an agent identified by a screening assay described herein), or a combination of such agents. In another embodiment, the method involves administering to a subject a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290,

21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 expression or activity.

[00320] Stimulation of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is desirable in situations in which 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is abnormally downregulated and/or in which increased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is likely to have a beneficial effect. Likewise, inhibition of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is desirable in situations in which 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is abnormally upregulated and/or in which decreased 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity is likely to have a beneficial effect.

[00321] The agents which modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity can be administered to a

subject using pharmaceutical compositions suitable for such administration. Such compositions typically comprise the agent (*e.g.*, nucleic acid molecule, protein, or antibody) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00322] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00323] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene

glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00324] Sterile injectable solutions can be prepared by incorporating the agent that modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity (*e.g.*, a fragment of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or an anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00325] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid

carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00326] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[00327] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00328] The agents that modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00329] In one embodiment, the agents that modulate 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

**[00330]** It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the agent that modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

**[00331]** Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Agents which exhibit large therapeutic indices are preferred. While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

**[00332]** The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulating agents lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any agent used in

the therapeutic methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[00333] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[00334] In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

[00335] The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500

grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

[00336] Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). It is furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[00337] Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa



chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[00338] The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[00339] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[00340] The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see, *e.g.*, Chen *et al.* (1994) *Proc. Natl.*

*Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

#### D. Pharmacogenomics

[00341] In conjunction with the therapeutic methods of the invention, pharmacogenomics (*i.e.*, the study of the relationship between a subject's genotype and that subject's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity, as well as tailoring the dosage and/or therapeutic regimen of treatment with an agent which modulates 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity.

[00342] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11): 983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate aminopeptidase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of

oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

[00343] One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

[00344] Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug target is known (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein used in the methods of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[00345] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and the cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These

polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

[00346] Alternatively, a method termed the "gene expression profiling" can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 molecule or 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator used in the methods of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

[00347] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of a subject. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and, thus, enhance therapeutic or prophylactic efficiency when treating a subject suffering from a hematological disease.

#### V. Recombinant Expression Vectors and Host Cells Used in the Methods of the Invention

[00348] The methods of the invention (*e.g.*, the screening assays described herein) include the use of vectors, preferably expression vectors, containing a nucleic acid encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899,

53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[00349] The recombinant expression vectors to be used in the methods of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel (1990) *Methods Enzymol.* 185:3-7. Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide

sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins, mutant forms of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins, fusion proteins, and the like).

[00350] The recombinant expression vectors to be used in the methods of the invention can be designed for expression of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins in prokaryotic or eukaryotic cells. For example, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel (1990) *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[00351] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the

fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[00352] Purified fusion proteins can be utilized in 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins. In a preferred embodiment, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six weeks).

[00353] In another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd ed.*, Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

[00354] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid).

[00355] The methods of the invention may further use a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific, or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

[00356] Another aspect of the invention pertains to the use of host cells into which a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecule of the invention is introduced, *e.g.*, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecule within a recombinant expression vector or a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecule containing sequences which allow it to homologously recombine into a specific site of the



host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[00357] A host cell can be any prokaryotic or eukaryotic cell. For example, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[00358] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

[00359] A host cell used in the methods of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Accordingly, the invention further provides methods for producing a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899,

53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein has been introduced) in a suitable medium such that a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein is produced. In another embodiment, the method further comprises isolating a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein from the medium or the host cell.

#### VI. Isolated Nucleic Acid Molecules Used in the Methods of the Invention

[00360] The methods of the invention include the use of isolated nucleic acid molecules that encode 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA) and fragments for use as PCR primers for the amplification or mutation of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

**[00361]** A nucleic acid molecule used in the methods of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, as a hybridization probe, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

**[00362]** Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79.

**[00363]** A nucleic acid used in the methods of the invention can be amplified using cDNA, mRNA or, alternatively, genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. Furthermore, oligonucleotides corresponding to 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

**[00364]** In a preferred embodiment, the isolated nucleic acid molecules used in the methods of the invention comprise the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, a complement of the nucleotide sequence

shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79 such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79 thereby forming a stable duplex.

[00365] In still another preferred embodiment, an isolated nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or a portion of any of this nucleotide sequence.

[00366] Moreover, the nucleic acid molecules used in the methods of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, *e.g.*, a biologically active portion of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19,

21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, of an anti-sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79. In one embodiment, a nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is greater than 100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, 1200-1300, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79.

[00367] As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7, 9 and 11. A preferred, non-limiting example of stringent hybridization conditions includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly stringent hybridization conditions includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced stringency hybridization conditions includes hybridization in 4X SSC, at about 50-60°C (or alternatively hybridization in 6X SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, *e.g.*, at 65-70°C or at 42-50°C are also intended to be encompassed by the

present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature ( $T_m$ ) of the hybrid, where  $T_m$  is determined according to the following equations. For hybrids less than 18 base pairs in length,  $T_m(^{\circ}\text{C}) = 2(\# \text{ of A} + \text{T bases}) + 4(\# \text{ of G} + \text{C bases})$ . For hybrids between 18 and 49 base pairs in length,  $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\% \text{G} + \text{C}) - (600/\text{N})$ , where N is the number of bases in the hybrid, and  $[\text{Na}^+]$  is the concentration of sodium ions in the hybridization buffer ( $[\text{Na}^+]$  for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M NaH<sub>2</sub>PO<sub>4</sub>, 7% SDS at about 65°C, followed by one or more washes at 0.02M NaH<sub>2</sub>PO<sub>4</sub>, 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

[00368] In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, such as by measuring a level of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662,

13913, 12405 or 5014 mRNA levels or determining whether a genomic 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene has been mutated or deleted.

**[00369]** The methods of the invention further encompass the use of nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, due to degeneracy of the genetic code and thus encode the same 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79. In another embodiment, an isolated nucleic acid molecule included in the methods of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80.

**[00370]** The methods of the invention further include the use of allelic variants of human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014, *e.g.*, functional and non-functional allelic variants. Functional allelic variants are naturally occurring amino acid sequence variants of the human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein that maintain a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54,

56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80, or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

**[00371]** Non-functional allelic variants are naturally occurring amino acid sequence variants of the human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein that do not have a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Non-functional allelic variants will typically contain a non-conservative substitution, deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80, or a substitution, insertion or deletion in critical residues or critical regions of the protein.

**[00372]** The methods of the present invention may further use non-human orthologues of the human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Orthologues of the human 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein are proteins that are isolated from non-human organisms and possess the same 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity.

**[00373]** The methods of the present invention further include the use of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, or a portion thereof, in which a mutation has been introduced. The mutation may lead to amino acid substitutions at "non-essential" amino acid residues or at "essential" amino acid residues. A "non-essential" amino acid residue is a residue



that can be altered from the wild-type sequence of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 (*e.g.*, the sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins of the present invention are not likely to be amenable to alteration.

**[00374]** Mutations can be introduced into SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side-chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014

coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using the assay described herein.

**[00375]** Another aspect of the invention pertains to the use of isolated nucleic acid molecules which are antisense to the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77 or 79. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding a 148, 302 or 567. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (also referred to as 5' and 3' untranslated regions).

**[00376]** Given the coding strand sequences encoding 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417,

57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine,

uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5- oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Antisense nucleic acid molecules used in the methods of the invention are further described above, in section IV.

[00377] In yet another embodiment, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules used in the methods of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci.* 93:14670-675.

[00378] PNAs of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules can be used in the therapeutic and diagnostic applications described herein. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600,

25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. *et al.* (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *supra*).

[00379] In another embodiment, PNAs of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. *et al.* (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. *et al.* (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

[00380] In other embodiments, the oligonucleotide used in the methods of the invention may include other appended groups such as peptides (*e.g.*, for targeting host cell

receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

VII. Isolated 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins and Anti-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 Antibodies Used in the Methods of the Invention

[00381] The methods of the invention include the use of isolated 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies. In one embodiment, native 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824,

28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

[00382] As used herein, a "biologically active portion" of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein includes a fragment of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein having a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity. Biologically active portions of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80, which include fewer amino acids than the full length 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins, and exhibit at least one activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844,

943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein (*e.g.*, the N-terminal region of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein that is believed to be involved in the regulation of apoptotic activity). A biologically active portion of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be a polypeptide which is, for example, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300 or more amino acids in length. Biologically active portions of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be used as targets for developing agents which modulate a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 activity.

[00383] In a preferred embodiment, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein used in the methods of the invention has an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80. In other embodiments, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein is



substantially identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80, and retains the functional activity of the protein of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection V above. Accordingly, in another embodiment, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein used in the methods of the invention is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80.

[00384] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80 having 500 amino acid residues, at least 75, preferably at least 150, more preferably at least 225, even more preferably at least 300, and even more preferably at least 400 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid

"identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[00385] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.* 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[00386] The methods of the invention may also use 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 chimeric or fusion proteins. As used herein, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 "chimeric protein" or "fusion protein" comprises a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide operatively linked to a non- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide. An " 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549,

9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 molecule, whereas a "non- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, *e.g.*, a protein which is different from the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein and which is derived from the same or a different organism. Within a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion protein the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide can correspond to all or a portion of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. In a preferred embodiment, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion protein comprises at least one biologically active portion of a 9118, 990, 17662, 81982, 630,

21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. In another preferred embodiment, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion protein comprises at least two biologically active portions of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide and the non-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide are fused in-frame to each other. The non-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide can be fused to the N-terminus or C-terminus of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide.

[00387] For example, in one embodiment, the fusion protein is a GST- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion protein in which the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences are fused to the C-terminus of the

GST sequences. Such fusion proteins can facilitate the purification of recombinant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014.

[00388] In another embodiment, this fusion protein is a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be increased through use of a heterologous signal sequence.

[00389] The 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion proteins used in the methods of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion proteins can be used to affect the bioavailability of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate. Use of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fusion proteins may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137,

13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. protein; (ii) mis-regulation of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene; and (iii) aberrant post-translational modification of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.

[00390] Moreover, the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-fusion proteins used in the methods of the invention can be used as immunogens to produce anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies in a subject, to purify 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 ligands and in screening assays to identify molecules which inhibit the interaction of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 substrate.

[00391] Preferably, a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 chimeric or fusion protein used in the methods of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-

frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.

[00392] The present invention also pertains to the use of variants of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins which function as either 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 agonists (mimetics) or as 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antagonists. Variants of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins can be generated by mutagenesis, *e.g.*,

discrete point mutation or truncation of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. An agonist of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. An antagonist of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can inhibit one or more of the activities of the naturally occurring form of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein by, for example, competitively modulating a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014-mediated activity of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.



[00393] In one embodiment, variants of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein which function as either 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 agonists (mimetics) or as 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein for 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein agonist or antagonist activity. In one embodiment, a variegated library of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of 9118, 990, 17662, 81982,

630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences therein. There are a variety of methods which can be used to produce libraries of potential 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

[00394] In addition, libraries of fragments of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein coding sequence can be used to generate a variegated population of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 fragments for screening and subsequent selection of variants of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052,

1521, 6662, 13913, 12405 or 5014 coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein.

**[00395]** Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

**[00396]** The methods of the present invention further include the use of anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014

antibodies. An isolated 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 using standard techniques for polyclonal and monoclonal antibody preparation. A full-length 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein can be used or, alternatively, antigenic peptide fragments of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be used as immunogens. The antigenic peptide of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78 or 80 and encompasses an epitope of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 such that an antibody raised against the peptide forms a specific immune complex with the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

[00397] Preferred epitopes encompassed by the antigenic peptide are regions of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

[00398] A 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 immunogen is typically used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse, or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein or a chemically synthesized 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 preparation induces a polyclonal anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody response.

[00399] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908,

14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')<sub>2</sub> fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 molecules. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. A monoclonal antibody composition thus typically displays a single binding affinity for a particular 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein with which it immunoreacts.

[00400] Polyclonal anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies can be prepared as described above by immunizing a suitable subject with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 immunogen. The anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908,

14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. If desired, the antibody molecules directed against 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014.

[00401] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* (1977) *supra*; Lerner (1981) *supra*; and Kenneth (1980) *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014, *e.g.*, using a standard ELISA assay.

[00402] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908,



14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 to thereby isolate immunoglobulin library members that bind 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* (1990) *Nature* 348:552-554.

[00403] Additionally, recombinant anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the methods of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT

International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

[00404] An anti-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody can be used to detect 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 protein. Anti- 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\alpha$ -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or

phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$ , or  $^3\text{H}$ .

[00405] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figure and the Sequence Listing is incorporated herein by reference.

## EXAMPLES

### EXAMPLE 1: TISSUE DISTRIBUTION OF USING TAOMAN™ ANALYSIS

[00406] This example describes the TaqMan™ procedure. The Taqman™ procedure is a quantitative, reverse transcription PCR-based approach for detecting

mRNA. The RT-PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold™ DNA

Polymerase to cleave a TaqMan™ probe during PCR. Briefly, cDNA was generated from the samples of interest, *e.g.*, heart, kidney, liver, skeletal muscle, and various vessels, and used as the starting material for PCR amplification. In addition to the 5' and 3' gene

specific primers, a gene-specific oligonucleotide probe (complementary to the region being amplified) was included in the reaction (*i.e.*, the Taqman™ probe). The TaqMan™ probe includes the oligonucleotide with a fluorescent reporter dye covalently linked to the 5' end of the probe (such as FAM (6-carboxyfluorescein), TET (6-carboxy-4,7,2,7-tetrachloro-6-fluoro-3,4-dihydroquinoline-2-carboxylic acid),

tetrachlorofluorescein), JOE (6-carboxy-4,5-dichloro-2,7-dimethoxyfluorescein), or VIC) and a quencher dye (TAMRA (6-carboxy-N,N,N',N'-tetramethylrhodamine) at the 3' end of the probe.

[00407] During the PCR reaction, cleavage of the probe separates the reporter dye and the quencher dye, resulting in increased fluorescence of the reporter. Accumulation of

PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of

interest is present, the probe specifically anneals between the forward and reverse primer sites. The 5'-3' nucleolytic activity of the AmpliTaq™ Gold DNA Polymerase cleaves the probe between the reporter and the quencher only if the probe hybridizes to the target. The

probe fragments are then displaced from the target, and polymerization of the strand continues. The 3' end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. RNA was prepared using the trizol method and treated with DNase to remove contaminating genomic DNA. cDNA was synthesized using standard techniques. Mock cDNA synthesis in the absence of reverse transcriptase resulted in samples with no detectable PCR amplification of the control gene confirms efficient removal of genomic DNA contamination.

#### Equivalents

[00408] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed:

1. A method for identifying a compound capable of treating a hematological disorder, comprising:
  - a) combining a compound to be tested with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide under conditions suitable for binding of the test compound to the polypeptide; and
  - b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating a hematological disorder.
2. The method of claim 1, wherein the compound is selected from the group consisting of a small molecule, a peptide or an antibody.
3. The method of claim 1, wherein the polypeptide further comprises heterologous sequences.
4. The method of claim 1, wherein the polypeptide is an isolated polypeptide, a membrane-bound form of an isolated polypeptide or a cell comprising the polypeptide.
5. The method of claim 4, wherein the cell is a hematological cell.
6. The method of claim 1, wherein the hematological disorder is a disorder associated with, but not limited to, anemia, neutropenia or thrombocytopenia.
7. The method of claim 1, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:
  - a) a competition binding assay;
  - b) an immunoassay; and
  - c) a yeast two-hybrid assay.

8. A method for identifying a compound capable of treating a hematological disorder, comprising:

- a) combining a compound to be tested with a host cell expressing a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide under conditions suitable for binding of the test compound to the polypeptide; and
- b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating a hematological disorder.

9. The method of claim 8, wherein the compound is selected from the group consisting of a small molecule, a peptide, an antibody or an antisense nucleic acid molecule.

10. The method of claim 8, wherein the polypeptide further comprises heterologous sequences.

11. The method of claim 8, wherein the host cell is a hematological cell.

12. The method of claim 8, wherein the hematological disorder is a disorder associated with, but not limited to, anemia, neutropenia or thrombocytopenia.

13. The method of claim 8, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- a) a competition binding assay;
- b) an immunoassay; and
- c) a yeast two-hybrid assay.

14. A method of identifying a subject having a hematological disorder, or at risk for developing a hematological disorder comprising:

- a) contacting a sample obtained from the subject comprising polypeptides with a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689,

28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding substance; and

b) detecting the presence of a polypeptide in the sample that binds to the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 binding substance, thereby identifying a subject having a hematological disorder, or at risk for developing a hematological disorder.

15. The method of claim 14, wherein the binding substance is an antibody.

16. The method of claim 14, wherein the binding substance is detectably labeled.

17. A method for treating a subject having a hematological disorder or a hematological disorder characterized by aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide activity or aberrant 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid expression comprising administering to the subject a 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator, thereby treating the subject having a hematological disorder.

18. The method of claim 17, wherein the disorder is a disorder associated with, but not limited to, anemia, neutropenia or thrombocytopenia .

19. The method of claim 17, wherein the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259,

21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator is administered in a pharmaceutically acceptable formulation.

20. The method of claim 17, wherein the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator is capable of modulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 polypeptide activity.

21. The method of claim 20, wherein the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator is an anti-9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 antibody.

22. The method of claim 17, wherein the 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 modulator is capable of modulating 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 nucleic acid expression.



## SEQUENCE LISTING

<110> Kelly, Louise M.  
Carroll, Joseph M.  
Farlow, Deborah  
Healy, Aileen

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9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891,  
9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947,  
53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 OR  
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Pro Leu Ala Glu Thr Thr Glu Asp Phe Trp Arg Met Leu Trp Glu His	
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aat tcc acc ata gtt gtg atg ctc acc aag ctg cgt gaa atg ggc aga	5406
Asn Ser Thr Ile Val Val Met Leu Thr Lys Leu Arg Glu Met Gly Arg	
1740 1745 1750	
gag aaa tgt cac caa tac tgg cca gca gaa cgg tct gca aga tac cag	5454
Glu Lys Cys His Gln Tyr Trp Pro Ala Glu Arg Ser Ala Arg Tyr Gln	
1755 1760 1765	
tac ttt gtt gta gat ccc atg gct gag tac aac atg cca cag tat atc	5502
Tyr Phe Val Val Asp Pro Met Ala Glu Tyr Asn Met Pro Gln Tyr Ile	
1770 1775 1780	
cta agg gaa ttc aag gtc aca gat gcc agg gac ggc cag tcc cga aca	5550
Leu Arg Glu Phe Lys Val Thr Asp Ala Arg Asp Gly Gln Ser Arg Thr	
1785 1790 1795	
gta agg cag ttc cag ttc act gac tgg cca gag caa gga gtg cca aag	5598
Val Arg Gln Phe Gln Phe Thr Asp Trp Pro Glu Gln Gly Val Pro Lys	
1800 1805 1810 1815	
tcc gga gaa gga ttt att gac ttc atc ggc caa gtc cat aaa aca aaa	5646
Ser Gly Glu Gly Phe Ile Asp Phe Ile Gly Gln Val His Lys Thr Lys	
1820 1825 1830	
gaa cag ttt ggc caa gat gga ccc att tca gtc cat tgc agc gcg ggc	5694
Glu Gln Phe Gly Gln Asp Gly Pro Ile Ser Val His Cys Ser Ala Gly	
1835 1840 1845	
gtt gga aga act gga gtc ttc ata acg cta agc att gtt ttg gaa aga	5742
Val Gly Arg Thr Gly Val Phe Ile Thr Leu Ser Ile Val Leu Glu Arg	
1850 1855 1860	
atg aga tat gaa gga gtt gta gat atc ttc cag act gtc aaa atg tta	5790
Met Arg Tyr Glu Gly Val Val Asp Ile Phe Gln Thr Val Lys Met Leu	
1865 1870 1875	
aga aca caa cga cca gct atg gta cag aca gag gat caa tat cag ttt	5838
Arg Thr Gln Arg Pro Ala Met Val Gln Thr Glu Asp Gln Tyr Gln Phe	
1880 1885 1890 1895	
tcc tat cgt gcc gca cta gag tac ctg ggc agc ttt gac cac tat gca	5886
Ser Tyr Arg Ala Ala Leu Glu Tyr Leu Gly Ser Phe Asp His Tyr Ala	
1900 1905 1910	
acg tag aaaccctga cccattctgg atttttacta caggcccttc aatatccatg	5942
Thr *	

gagtccttc tgagccatac agggcacttg agaagtcctt cttaacttct agctaacaac 6002  
 tacttagtgg gactattaca cacaaaacaa attaaaaaca aattattcca ggtggaccaa 6062  
 gaattctttg acatcgcccc ttcccacccat actgctcata ataacatttt aggggccaag 6122  
 gggagggaat gtttaaaaag aaagtccttg atttagtttt ttagtattgt aaagatactg 6182  
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<211> 1912

<212> PRT

<213> Homo sapiens

<400> 64

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			20					25				30		Asp
Gln	Thr	Gly	Val	Ser	Gly	Gly	Val	Ala	Ser	Phe	Ile	Cys	Gln	Ala
		35					40					45		Thr
Gly	Asp	Pro	Arg	Pro	Lys	Ile	Val	Trp	Asn	Lys	Lys	Gly	Lys	Val
	50					55					60			
Ser	Asn	Gln	Arg	Phe	Glu	Val	Ile	Glu	Phe	Asp	Asp	Gly	Ser	Gly
	65				70					75			80	Ser
Val	Leu	Arg	Ile	Gln	Pro	Leu	Arg	Thr	Pro	Arg	Asp	Glu	Ala	Ile
			85						90				95	Tyr
Glu	Cys	Val	Ala	Ser	Asn	Asn	Val	Gly	Glu	Ile	Ser	Val	Ser	Thr
			100					105					110	Arg
Leu	Thr	Val	Leu	Arg	Glu	Asp	Gln	Ile	Pro	Arg	Gly	Phe	Pro	Thr
	115						120					125		Ile
Asp	Met	Gly	Pro	Gln	Leu	Lys	Val	Glu	Arg	Thr	Arg	Thr	Ala	Thr
	130					135					140			
Met	Leu	Cys	Ala	Ala	Ser	Gly	Asn	Pro	Asp	Pro	Glu	Ile	Thr	Phe
	145				150					155				160
Lys	Asp	Phe	Leu	Pro	Val	Asp	Thr	Ser	Asn	Asn	Asn	Gly	Arg	Ile
			165						170				175	Lys
Gln	Leu	Arg	Ser	Glu	Ser	Ile	Gly	Gly	Thr	Pro	Ile	Arg	Gly	Ala
			180					185					190	Leu
Gln	Ile	Glu	Gln	Ser	Glu	Glu	Ser	Asp	Gln	Gly	Lys	Tyr	Glu	Cys
	195						200					205		Val
Ala	Thr	Asn	Ser	Ala	Gly	Thr	Arg	Tyr	Ser	Ala	Pro	Ala	Asn	Leu
	210					215					220			Tyr
Val	Arg	Glu	Leu	Arg	Glu	Val	Arg	Arg	Val	Pro	Pro	Arg	Phe	Ser
	225				230					235				Ile
Pro	Pro	Thr	Asn	His	Glu	Ile	Met	Pro	Gly	Gly	Ser	Val	Asn	Ile
			245						250				255	Thr
Cys	Val	Ala	Val	Gly	Ser	Pro	Met	Pro	Tyr	Val	Lys	Trp	Met	Leu
			260					265					270	Gly
Ala	Glu	Asp	Leu	Thr	Pro	Glu	Asp	Met	Pro	Ile	Gly	Arg	Asn	Val
	275						280				285			
Leu	Glu	Leu	Asn	Asp	Val	Arg	Gln	Ser	Ala	Asn	Tyr	Thr	Cys	Val
	290					295					300			Ala
Met	Ser	Thr	Leu	Gly	Val	Ile	Glu	Ala	Ile	Ala	Gln	Ile	Thr	Val
	305				310					315				Lys
Ala	Leu	Pro	Lys	Pro	Pro	Gly	Thr	Pro	Val	Val	Thr	Glu	Ser	Thr
			325						330					Ala
Thr	Ser	Ile	Thr	Leu	Thr	Trp	Asp	Ser	Gly	Asn	Pro	Glu	Pro	Val
			340					345					350	Ser
Tyr	Tyr	Ile	Gln	His	Lys	Pro	Lys	Asn	Ser	Glu	Glu	Leu	Tyr	Lys
		355				360						365		

Glu Ile Asp Gly Val Ala Thr Thr Arg Tyr Ser Val Ala Gly Leu Ser  
 370 375 380  
 Pro Tyr Ser Asp Tyr Glu Phe Arg Val Val Ala Val Asn Asn Ile Gly  
 385 390 395 400  
 Arg Gly Pro Pro Ser Glu Pro Val Leu Thr Gln Thr Ser Glu Gln Ala  
 405 410 415  
 Pro Ser Ser Ala Pro Arg Asp Val Gln Ala Arg Met Leu Ser Ser Thr  
 420 425 430  
 Thr Ile Leu Val Gln Trp Lys Glu Pro Glu Glu Pro Asn Gly Gln Ile  
 435 440 445  
 Gln Gly Tyr Arg Val Tyr Tyr Thr Met Asp Pro Thr Gln His Val Asn  
 450 455 460  
 Asn Trp Met Lys His Asn Val Ala Asp Ser Gln Ile Thr Thr Ile Gly  
 465 470 475 480  
 Asn Leu Val Pro Gln Lys Thr Tyr Ser Val Lys Val Leu Ala Phe Thr  
 485 490 495  
 Ser Ile Gly Asp Gly Pro Leu Ser Ser Asp Ile Gln Val Ile Thr Gln  
 500 505 510  
 Thr Gly Val Pro Gly Gln Pro Leu Asn Phe Lys Ala Glu Pro Glu Ser  
 515 520 525  
 Glu Thr Ser Ile Leu Leu Ser Trp Thr Pro Pro Arg Ser Asp Thr Ile  
 530 535 540  
 Ala Asn Tyr Glu Leu Val Tyr Lys Asp Gly Glu His Gly Glu Glu Gln  
 545 550 555 560  
 Arg Ile Thr Ile Glu Pro Gly Thr Ser Tyr Arg Leu Gln Gly Leu Lys  
 565 570 575  
 Pro Asn Ser Leu Tyr Tyr Phe Arg Leu Ala Ala Arg Ser Pro Gln Gly  
 580 585 590  
 Leu Gly Ala Ser Thr Ala Glu Ile Ser Ala Arg Thr Met Gln Ser Lys  
 595 600 605  
 Pro Ser Ala Pro Pro Gln Asp Ile Ser Cys Thr Ser Pro Ser Ser Thr  
 610 615 620  
 Ser Ile Leu Val Ser Trp Gln Pro Pro Pro Val Glu Lys Gln Asn Gly  
 625 630 635 640  
 Ile Ile Thr Glu Tyr Ser Ile Lys Tyr Thr Ala Val Asp Gly Glu Asp  
 645 650 655  
 Asp Lys Pro His Glu Ile Leu Gly Ile Pro Ser Asp Thr Thr Lys Tyr  
 660 665 670  
 Leu Leu Glu Gln Leu Glu Lys Trp Thr Glu Tyr Arg Ile Thr Val Thr  
 675 680 685  
 Ala His Thr Asp Val Gly Pro Gly Pro Glu Ser Leu Ser Val Leu Ile  
 690 695 700  
 Arg Thr Asn Glu Asp Val Pro Ser Gly Pro Pro Arg Lys Val Glu Val  
 705 710 715 720  
 Glu Ala Val Asn Ser Thr Ser Val Lys Val Ser Trp Arg Ser Pro Val  
 725 730 735  
 Pro Asn Lys Gln His Gly Gln Ile Arg Gly Tyr Gln Val His Tyr Val  
 740 745 750  
 Arg Met Glu Asn Gly Glu Pro Lys Gly Gln Pro Met Leu Lys Asp Val  
 755 760 765  
 Met Leu Ala Asp Ala Gln Trp Glu Phe Asp Asp Thr Thr Glu His Asp  
 770 775 780  
 Met Ile Ile Ser Gly Leu Gln Pro Glu Thr Ser Tyr Ser Leu Thr Val  
 785 790 795 800  
 Thr Ala Tyr Thr Thr Lys Gly Asp Gly Ala Arg Ser Lys Pro Lys Leu  
 805 810 815  
 Val Ser Thr Thr Gly Ala Val Pro Gly Lys Pro Arg Leu Val Ile Asn  
 820 825 830  
 His Thr Gln Met Asn Thr Ala Leu Ile Gln Trp His Pro Pro Val Asp  
 835 840 845  
 Thr Phe Gly Pro Leu Gln Gly Tyr Arg Leu Lys Phe Gly Arg Lys Asp

850	855	860
Met Glu Pro Leu Thr Thr Leu Glu Phe Ser Glu Lys Glu Asp His Phe		
865	870	875
Thr Ala Thr Asp Ile His Lys Gly Ala Ser Tyr Val Phe Arg Leu Ser		880
	885	890
Ala Arg Asn Lys Val Gly Phe Gly Glu Met Val Lys Glu Ile Ser		895
	900	905
Ile Pro Glu Glu Val Pro Thr Gly Phe Pro Gln Asn Leu His Ser Glu		910
	915	920
Gly Thr Thr Ser Thr Ser Val Gln Leu Ser Trp Gln Pro Pro Val Leu		925
	930	935
Ala Glu Arg Asn Gly Ile Ile Thr Lys Tyr Thr Leu Leu Tyr Arg Asp		940
945	950	955
Ile Asn Ile Pro Leu Leu Pro Met Glu Gln Leu Ile Val Pro Ala Asp		960
	965	970
Thr Thr Met Thr Leu Thr Gly Leu Lys Pro Asp Thr Thr Tyr Asp Val		975
	980	985
Lys Val Arg Ala His Thr Ser Lys Gly Pro Gly Pro Tyr Ser Pro Ser		990
	995	1000
Val Gln Phe Arg Thr Leu Pro Val Asp Gln Val Phe Ala Lys Asn Phe		1005
	1010	1015
His Val Lys Ala Val Met Lys Thr Ser Val Leu Leu Ser Trp Glu Ile		1020
1025	1030	1035
Pro Glu Asn Tyr Asn Ser Ala Met Pro Phe Lys Ile Leu Tyr Asp Asp		1040
	1045	1050
Gly Lys Met Val Glu Glu Val Asp Gly Arg Ala Thr Gln Lys Leu Ile		1055
	1060	1065
Val Asn Leu Lys Pro Glu Lys Ser Tyr Ser Phe Val Leu Thr Asn Arg		1070
	1075	1080
Gly Asn Ser Ala Gly Gly Leu Gln His Arg Val Thr Ala Lys Thr Ala		1085
	1090	1095
Pro Asp Val Leu Arg Thr Lys Pro Ala Phe Ile Gly Lys Thr Asn Leu		1100
1105	1110	1115
Asp Gly Met Ile Thr Val Gln Leu Pro Glu Val Pro Ala Asn Glu Asn		1120
	1125	1130
Ile Lys Gly Tyr Tyr Ile Ile Ile Val Pro Leu Lys Lys Ser Arg Gly		1135
	1140	1145
Lys Phe Ile Lys Pro Trp Glu Ser Pro Asp Glu Met Glu Leu Asp Glu		1150
	1155	1160
Leu Leu Lys Glu Ile Ser Arg Lys Arg Arg Ser Ile Arg Tyr Gly Arg		1165
	1170	1175
Glu Val Glu Leu Lys Pro Tyr Ile Ala Ala His Phe Asp Val Leu Pro		1180
1185	1190	1195
Thr Glu Phe Thr Leu Gly Asp Asp Lys His Tyr Gly Gly Phe Thr Asn		1200
	1205	1210
Lys Gln Leu Gln Ser Gly Gln Glu Tyr Val Phe Phe Val Leu Ala Val		1215
	1220	1225
Met Glu His Ala Glu Ser Lys Met Tyr Ala Thr Ser Pro Tyr Ser Asp		1230
	1235	1240
Pro Val Val Ser Met Asp Leu Asp Pro Gln Pro Ile Thr Asp Glu Glu		1245
	1250	1255
Glu Gly Leu Ile Trp Val Val Gly Pro Val Leu Ala Val Val Phe Ile		1260
1265	1270	1275
Ile Cys Ile Val Ile Ala Ile Leu Leu Tyr Lys Arg Lys Arg Ala Glu		1280
	1285	1290
Ser Asp Ser Arg Lys Ser Ser Ile Pro Asn Asn Lys Glu Ile Pro Ser		1295
	1300	1305
His His Pro Thr Asp Pro Val Glu Leu Arg Arg Leu Asn Phe Gln Thr		1310
	1315	1320
Pro Gly Met Ala Ser His Pro Pro Ile Pro Ile Leu Glu Leu Ala Asp		1325
1330	1335	1340

His Ile Glu Arg Leu Lys Ala Asn Asp Asn Leu Lys Phe Ser Gln Glu  
 1345 1350 1355 1360  
 Tyr Glu Ser Ile Asp Pro Gly Gln Gln Phe Thr Trp Glu His Ser Asn  
 1365 1370 1375  
 Leu Glu Val Asn Lys Pro Lys Asn Arg Tyr Ala Asn Val Ile Ala Tyr  
 1380 1385 1390  
 Asp His Ser Arg Val Leu Leu Ser Ala Ile Glu Gly Ile Pro Gly Ser  
 1395 1400 1405  
 Asp Tyr Val Asn Ala Asn Tyr Ile Asp Gly Tyr Arg Lys Gln Asn Ala  
 1410 1415 1420  
 Tyr Ile Ala Thr Gln Gly Ser Leu Pro Glu Thr Phe Gly Asp Phe Trp  
 1425 1430 1435 1440  
 Arg Met Ile Trp Glu Gln Arg Ser Ala Thr Val Val Met Met Thr Lys  
 1445 1450 1455  
 Leu Glu Glu Arg Ser Arg Val Lys Cys Asp Gln Tyr Trp Pro Ser Arg  
 1460 1465 1470  
 Gly Thr Glu Thr His Gly Leu Val Gln Val Thr Leu Leu Asp Thr Val  
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 Glu Leu Ala Thr Tyr Cys Val Arg Thr Phe Ala Leu Tyr Lys Asn Gly  
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 Ser Ser Glu Lys Arg Glu Val Arg Gln Phe Gln Phe Thr Ala Trp Pro  
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 Asp His Gly Val Pro Glu His Pro Thr Pro Phe Leu Ala Phe Leu Arg  
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 Arg Val Lys Thr Cys Asn Pro Pro Asp Ala Gly Pro Met Val Val His  
 1540 1545 1550  
 Cys Ser Ala Gly Val Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala  
 1555 1560 1565  
 Met Leu Glu Arg Ile Lys His Glu Lys Thr Val Asp Ile Tyr Gly His  
 1570 1575 1580  
 Val Thr Leu Met Arg Ala Gln Arg Asn Tyr Met Val Gln Thr Glu Asp  
 1585 1590 1595 1600  
 Gln Tyr Ile Phe Ile His Asp Ala Leu Leu Glu Ala Val Thr Cys Gly  
 1605 1610 1615  
 Asn Thr Glu Val Pro Ala Arg Asn Leu Tyr Ala Tyr Ile Gln Lys Leu  
 1620 1625 1630  
 Thr Gln Ile Glu Thr Gly Glu Asn Val Thr Gly Met Glu Leu Glu Phe  
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 Lys Arg Leu Ala Ser Ser Lys Ala His Thr Ser Arg Phe Ile Ser Ala  
 1650 1655 1660  
 Asn Leu Pro Cys Asn Lys Phe Lys Asn Arg Leu Val Asn Ile Met Pro  
 1665 1670 1675 1680  
 Tyr Glu Ser Thr Arg Val Cys Leu Gln Pro Ile Arg Gly Val Glu Gly  
 1685 1690 1695  
 Ser Asp Tyr Ile Asn Ala Ser Phe Ile Asp Gly Tyr Arg Gln Gln Lys  
 1700 1705 1710  
 Ala Tyr Ile Ala Thr Gln Gly Pro Leu Ala Glu Thr Thr Glu Asp Phe  
 1715 1720 1725  
 Trp Arg Met Leu Trp Glu His Asn Ser Thr Ile Val Val Met Leu Thr  
 1730 1735 1740  
 Lys Leu Arg Glu Met Gly Arg Glu Lys Cys His Gln Tyr Trp Pro Ala  
 1745 1750 1755 1760  
 Glu Arg Ser Ala Arg Tyr Gln Tyr Phe Val Val Asp Pro Met Ala Glu  
 1765 1770 1775  
 Tyr Asn Met Pro Gln Tyr Ile Leu Arg Glu Phe Lys Val Thr Asp Ala  
 1780 1785 1790  
 Arg Asp Gly Gln Ser Arg Thr Val Arg Gln Phe Gln Phe Thr Asp Trp  
 1795 1800 1805  
 Pro Glu Gln Gly Val Pro Lys Ser Gly Glu Gly Phe Ile Asp Phe Ile  
 1810 1815 1820  
 Gly Gln Val His Lys Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile

1825                      1830                      1835                      1840  
 Ser Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr  
                                  1845                      1850                      1855  
 Leu Ser Ile Val Leu Glu Arg Met Arg Tyr Glu Gly Val Val Asp Ile  
                                  1860                      1865                      1870  
 Phe Gln Thr Val Lys Met Leu Arg Thr Gln Arg Pro Ala Met Val Gln  
                                  1875                      1880                      1885  
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 Gly Ser Phe Asp His Tyr Ala Thr  
 1905                      1910

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 Met Arg Pro Ala Pro Ile Ala Leu Trp Leu Arg Leu Val Leu Ala Leu  
   1                                  5                                  10                                  15  
  
 gcc ctt gtc cgc ccc cgg gct gtg ggg tgg gcc ccg gtc cga gcc ccc 156  
 Ala Leu Val Arg Pro Arg Ala Val Gly Trp Ala Pro Val Arg Ala Pro  
                                   20                                  25                                  30  
  
 atc tat gtc agc agc tgg gcc gtc cag gtg tcc cag ggt aac cgg gag 204  
 Ile Tyr Val Ser Ser Trp Ala Val Gln Val Ser Gln Gly Asn Arg Glu  
                                   35                                  40                                  45  
  
 gtc gag cgc ctg gca cgc aaa ttc ggc ttc gtc aac ctg ggg ccg atc 252  
 Val Glu Arg Leu Ala Arg Lys Phe Gly Phe Val Asn Leu Gly Pro Ile  
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 Phe Pro Asp Gly Gln Tyr Phe His Leu Arg His Arg Gly Val Val Gln  
                                   65                                  70                                  75                                  80  
  
 cag tcc ctg acc ccg cac tgg ggc cac cgc ctg cac ctg aag aaa aac 348  
 Gln Ser Leu Thr Pro His Trp Gly His Arg Leu His Leu Lys Lys Asn  
                                   85                                  90                                  95  
  
 ccc aag gtg cag tgg ttc cag cag cag acg ctg cag cgg cgg gtg aaa 396  
 Pro Lys Val Gln Trp Phe Gln Gln Gln Thr Leu Gln Arg Arg Val Lys  
                                   100                                  105                                  110  
  
 cgc tct gtc gtg gtg ccc acg gac ccc tgg ttc tcc aag cag tgg tac 444  
 Arg Ser Val Val Val Pro Thr Asp Pro Trp Phe Ser Lys Gln Trp Tyr  
                                   115                                  120                                  125  
  
 atg aac agc gag gcc caa cca gac ctg agc atc ctg cag gcc tgg agt 492  
 Met Asn Ser Glu Ala Gln Pro Asp Leu Ser Ile Leu Gln Ala Trp Ser  
                                   130                                  135                                  140  
  
 cag ggg ctg tca ggc cag ggc atc gtg gtc tct gtg ctg gac gat ggc 540